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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,319	BARTLETT ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1 and 4-13 (each in part)) in the Response filed 24 December 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims **2, 3,** and **14-20** are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claim Objections

2. Claims **8, 9,** and **13** are objected to because of the following informalities: said claims depend from non-elected claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims **1** and **4-13** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

4. The claims are drawn very broadly to a method of facilitating regeneration, growth, and/or development of a central nervous system in any given animal (including birds) via increasing, elevating, or otherwise enhancing the levels of a Eph receptor or its functional equivalent or a ligand thereof. The language of said claims encompasses three broad categories of activity in the absence of examples.

5. The specification teaches that axon guidance involves molecules including but not limited to Eph receptors and their ligands, ephrins. Said molecules are also involved in the development of the visual system and other developmental events such as axonal fasciculation and establishing brain commissures.

6. The specification fails to provide any guidance for the successful regeneration, growth, and/or development in any animal (including birds) via increasing, elevating, or otherwise enhancing the levels of a Eph receptor, its functional equivalent, or any ligand, and since resolution of the various complications in regards to targeting the role a particular gene in an organism in regeneration, growth, and development in the central nervous system (CNS) is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of agents that have the required activity, isolation, characterization, and then extensive and unguided experimentation to correlate with regeneration, growth, and development in the CNS

via an Eph receptor, its functional equivalent, or its ligand. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

7. No nexus between any known disease state or condition and Eph receptors, their functional equivalents, or ligands has been established. This leaves the skilled artisan to undertake undue experimentation to first identify the conditions, confirm the involvement of any given Eph receptors, their functional equivalents, or ligands in a rate-determining-step in the so identified disease or condition and then under take further undue experimentation to isolate or synthesis, then characterize an agent which has the desired properties of affecting the Eph receptors, their functional equivalents, or ligands in such a way as to fulfill the preamble of claim 1.

8. Additionally, a person skilled in the art would recognize that predicting the efficacy of using an as of yet identified and characterized agent *in vivo* based solely the role of Eph receptors in development is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo*, such a disclosure would not be considered enabling since the state of regeneration, growth, and development in the CNS is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

9. The following references are cited herein to illustrate the state of the art of Eph receptors and the CNS.

10. Regarding the breadth of the claims, the art teaches that the CNS is a hostile environment to regeneration and growth. The art recognizes that development is limited to embryonic and early juvenile period after which it is no longer possible in higher vertebrates such as mammals and birds. Jackowski (1995) "Neural injury repair: hope for the future as barriers to effective CNS regeneration become clearer." British Journal of Neurosurgery **9**: 303-317 teaches that two barriers prevent regeneration, growth, and repair in the central nervous system (CNS): an intrinsic inability of CNS neurons to mount a regenerative response and a CNS environment that is non-supportive or actively inhibitory to neural regeneration (pp. 305-311). Therefore the claims as instantly presented run contrary to the teaching of the art where "regeneration", "growth", and "development" in the CNS have high hurdles to overcome. The instant Specification does not teach nor adequately address how the skilled artisan is to surmount these obstacles when practicing the invention.

11. Also on the breadth of the claims, Lickliter *et al.* (January 1996) "Embryonic stem cell express multiple Eph-subfamily receptor tyrosine kinases." PNAS **93**: 145-150 teaches that Eph and its homology form the largest subfamily of receptor kinases (pp. 145). Lickliter *et al.* also teaches that the role/function of Eph receptors in adult animals is not known (pp. 149). Thus the skilled artisan is confronted with a massive genus and an inadequate disclosure of a representative number of species with which to practice the invention as claimed.

12. On the nature of the invention, no agent or compound or molecule has been disclosed that has any activity on Eph receptors, their functional equivalent, or their ligand in effect extending an invitation of experimentation to the skilled artisan. Zhang *et al.* (15 November 1996) "Detection of Ligands in regions Anatomically Connected to Neurons Expressing the Eph Receptor Bsk: Potential Roles in Neuron-Target Interaction." The Journal of Neuroscience **16**(22): 7182-7192 teaches that Bsk, a member of the Eph receptor family, interacts with any number of the seven candidate ligands of the Eph family (pp. 7182). The Eph family ligands also show a distinct yet overlapping pattern of expression (Table 1). Zhang *et al.* teach that the ligands may work alone or in concert with others to exert their effects thus resulting in a complex web of ligand and Eph receptor interactions.

13. On the state of the prior art, Castellani *et al.* (15 June 1998) "Dual Action of a Ligand for Eph Receptor Tyrosine Kinases on Specific Populations of Axons during the Development of Cortical Circuits." The Journal of Neuroscience **18**(12): 4663-4672 teaches that ephrins are ligands for the Eph receptor (pp. 4663). The ephrins repel axon guidance and define inhibitory territories for axon innervation. These ligands can differ in their effects. For instance, ephrin-A5 exerts differential effects on the growth, guidance, and branch formation of distinct populations of cortical axons (Figure 5). Castellani *et al.* teaches that ephrin-A5 is a repulsive signal for certain subpopulations of cortical neurons but is a promoter of axon collateral formation for others (pp. 4670-4671). Therefore the art teaches that the ligands of the Eph receptor can have contradictory effects on different neurons leaving a complex situation of the skilled artisan to untangle.

14. On the level of predictability, the CNS is a complex and unpredictable medium in which to practice the claimed invention [see Kandel (2002) "Principles in Neural Science." 4th Ed. Chapter 2 Nerve Cells and Behavior (pp. 19-35); Brückner & Klein (June 1998) "Signaling by Eph receptor and their ephrin ligands." Current Opinion in Neurobiology **8**(3): 375-382 (Figure 1); Pasquale (October 1997) "The Eph Family of receptors." Current Opinion in Cell Biology **9**(5): 608-615 (Table 1-3)]. Holder & Klein (1999) "Eph receptors and ephrins: effectors of morphogenesis." Development **126**: 2033-2044 teaches that Eph receptors and ephrins (the ligands thereof) are expressed in a wide range of regions in the vertebrate embryo (pp. 2033). Also the function of Eph receptors and ephrins covers a broad range of activities including but not limited to segmentation of the somites and rhombomeres, the formation of blood vessels, axonal guidance, migration of the neural crest and metastasis of transformed cells, and cellular morphology (pp. 2041). Therefore the skilled artisan is presented with a massive genus of receptors and ligands which are expressed in a wide range of tissues, each of which, receptor and ligand coupling, have diverse functions.

15. On the amount of direction provided by the inventor, only three ligands, ephirn-B1, B2, and B3 as well as two Eph receptor families EphA EphB are provided. No specific structure or mechanism by which either works or must be affected is disclosed to offer guidance to fulfill the goal of the preamble.

16. The Specification as filed is silent on working examples to practice the claimed invention. The Specification as filed is also silent on the nature and structure of functional equivalents of Eph receptors. Jensen (2000) "Eph Receptors and Ephrins." Stem Cells **18**: 63-64 teaches 14 Eph receptors. Some Eph receptors such as EphB5 and EphB6 have no known ligands

while others have up to 6 ligands such as EphA3 (Table 1). Therefore the skilled artisan is not shown with Eph receptor or "equivalent" in the face of the largest tyrosine kinase receptor subfamily known.

17. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from prophetic suggestion the absence of guidance to the *in vivo* practice of the invention as claimed as exemplified in the references herein.

18. Claims **1** and **4-9** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

19. Claim 1 recites "functional equivalent" but does not require that the functional equivalent to possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of agents that is defined by equivalence to a known Eph receptor.

20. Claim 1 also recites a method without disclosing the agent which is administered to achieve the effect. Thus the claim requires the skilled artisan to undertake undue experimentation to identify an agent, which the art recognizes can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds, that will accomplish the preamble of claim 1.

21. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the product to be used in the method, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is in the form of a recitation of a desired outcome. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

22. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

23. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003). In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since patent described the compound's desired function of reducing activity of enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect, but patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound, since specification did not indicate that compounds are available in public depository, since claimed treatment method cannot be practiced without compound, and since inventors thus cannot be said to have "possessed" claimed invention without knowing of compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

24. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

25. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

§ 2172.01. The omitted steps are: how Eph receptor or its functional equivalent or a ligand thereof is elevated or otherwise enhanced.

26. Claim **1** is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: what constitutes a functional equivalent of an Eph receptor.

27. Claims **1** and **6-13** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "animal or bird" is unclear since the Examiner is not aware of any birds which are not animals (see American Heritage Dictionary definitions of "animal" and "bird" included herein). Therefore the metes and bounds of the phrase "animal or bird" is not clearly defined.

Summary

28. No claims are allowed.

29. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

a. Zisch & Pasquale (1997) "The Eph Family: a multitude of receptors that mediate cell recognition signals." Cell and Tissue Research **290**(2): 217-226

b. Orioli & Klein (September 1997) "The Eph receptor family: axonal guidance by contact repulsion." Trends Genet. **13**(9): 354-359

c. Flanagan & Vanderhaeghen (1998) "The ephrins and Eph receptors in neural development." Annual Review of Neuroscience **21**: 309-345

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
February 5, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER